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Formulation and Evaluation of Propranolol Hydrochloride Loaded Mucoadhesive Microspheres

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ABSTRACT

Propranolol hydrochloride is a beta blocking agent which is used for the treatment of hypertension and it is highly lipophilic and completely absorbed after oral administration. The present study, Propranolol hydrochloride Mucoadhesive microspheres were formulated using sodium alginate and the different concentration of polymers like Xanthan gum and Guar gum by ionic gelation technique with an aim to controlled release and improve bioavailability. Six formulations were prepared by using different drug to polymer ratios, and evaluated for relevant parameters. Depending upon the drug to polymer ratio, the percentage yield is found between 51.06±0.51% to 72.42±0.83 % in all formulations. The surface morphology of the microspheres was characterized by SEM. The prepared microspheres were discrete, spherical in shape and showed free flowing properties. The mean particle size of microspheres significantly increases with increasing polymer concentration and it was in the range between 23.10±0.12 µm to 33.66±0.41 µm. Among all the formulation, XG-III showed a high drug entrapment efficiency of 68.28±0.53 % and highest percentage swelling index of 67.75±0.06 %. The *in-vitro* drug release studies revealed that XG-III formulation is controlled and found to be 86.8±0.20 % and GG-III is found to be 89.8±0.11 % at the end of dissolution studies. The mechanism of drug release was evaluated using the linear regression coefficient. Stability studies of selected formulation showed good results. It could be also concluding that the all the formulations were shown satisfactory results and suitable for potential therapeutic uses.

Keywords: Propranolol hydrochloride, Mucoadhesive Microspheres, Xanthan gum, Guar gum, *In-vitro* drug release, Stability studies.

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INTRODUCTION

An oral drug delivery is the most convenient drug delivery to systemic circulation but it has short-term limitations and frequently essential to take several times a day results in a fluctuated drug level and have been reported to covering pre-systemic elimination by gastrointestinal degradation due to low systemic bioavailability results short duration of action and undesirable toxicity which may reduce patient compliance[1]. It can be overcome by controlled drug delivery systems such as microsphere formulation is advantageous to have means for providing an intimate contact of the drug delivery with the absorbing membranes. This can be achieved by coupling mucoadhesion characteristics to microspheres provide an efficient absorption of drugs and enhanced bioavailability owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer. Such mucoadhesive drug delivery systems utilized the property of mucoadhesion of certain polymers which become adhesive on hydration and used for targeting a drug to particular region of the body. It provides the possibility of avoiding either destruction by gastrointestinal contents and or hepatic first-pass inactivation of the drug, decrease dosing frequency and exhibit a prolonged residence time with the absorption site and produce prolonging its effect than conventional dosage forms[2-4].

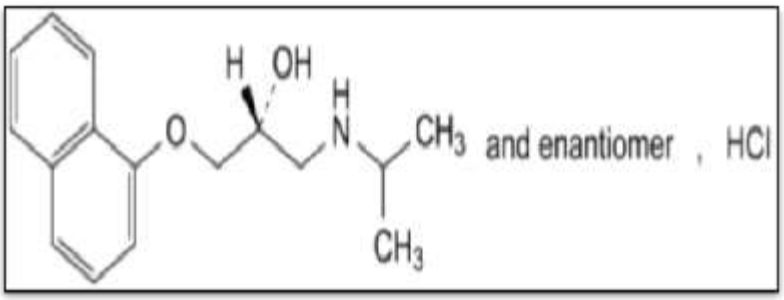

Figure 1: Structure of Propranolol Hydrochloride

Propranolol hydrochloride is a beta blocker (Figure 1), widely used in the treatment weak and moderate hypertension, angina pectoris and ventricular arrhythmia etc[5-7]. It is highly lipophilic and has oral bioavailability is approximately 26% and undergoes high first-pass metabolism by liver and 90% of circulating propranolol is bound to plasma proteins and most metabolites appearing in the urine. Half-life is almost 3-4 hours necessitates the need for multiple doses administration (3-4 times) of 40-80mg/day[8]. Due to the short half-life, propranolol hydrochloride is a very good candidate for mucoadhesive drug delivery system to prolong gastric residence time into the stomach which enhances bioavailability and reduce its doses and toxicity. So it's necessary to develop mucoadhesive microspheres from naturally occurring polymers, which

adhere to the mucosa and release the drug in slow and controlled manner and there by controlling the hypertension. This study is an attempt to prepare mucoadhesive microspheres loaded propranolol hydrochloride using natural gums with varying ratios and evaluate the characterization.

MATERIALS AND METHOD

Materials:

Propranolol Hydrochloride was obtained from Yarrow Chem Products, Mumbai, India. Sodium alginate and xanthan gum from Qualigens Fine Chem Pvt Ltd, Mumbai, India, Guar gum from Yarrow Chem Products, Mumbai, India, Calcium chloride from Flora Chemicals, India.

IR spectral analysis:

FT-IR spectrum of Propranolol Hcl and polymers was recorded using KBr mixing method on the FT-IR instrument (Schimadzu FTIR instrument). The drug alone and drug in combination with polymers in the ratio of 1:1 was taken and subjected to FT-IR studies [9].

Preparation of Mucoadhesive Microspheres of Propranolol Hydrochloride (Hcl):

The Microspheres were prepared by using different ratios of Propranalol Hcl, sodium alginate, guar gum and xanthan gum. Sodium alginate was dissolved in deionized water to form a homogeneous solution (2 % w/v). Guar gum and xanthan gum were dissolved separately with deionized water to get viscous and sticky solutions. The pure drug was dispersed in the solution of gum and then sodium alginate solution was added to it with vigorous stirring until formation of an even dispersion. The resulting dispersion was then extruded drop wise into the 100 ml calcium chloride solution (10 % w/v) through a 23G syringe. The formed beads were retained in the calcium chloride solution for 15 minutes to complete the formation of spherical rigid microspheres. They were collected by decantation, washed and dried at room temperature and subsequently stored in desiccators. Six formulations were prepared by different ratios of drug and polymer as given in Table 1 and were evaluated for relevant parameters[10].

Table 1: Composition of Propranolol Hcl Mucoadhesive Microspheres

Formulations code	Propranolol Hcl (mg)	Sodium Alginate(% w/v)	Guar gum(%w/v)	Xanthan Gum (% w/v)	Calcium Chloride (% w/v)
XG-I	100	2	-	0.25	10
XG-II	100	2	-	0.5	10
XG-III	100	2	-	0.75	10
GG-I	100	2	0.25	-	10
GG-II	100	2	0.5	-	10
GG-III	100	2	0.75	-	10

Characterization of Mucoadhesive Microspheres

Micromeritic Properties:

Mucoadhesive microspheres were characterized by their micromeritic properties like bulk density, tapped density, carr's index, hausner's ratio and angle of repose[11-12].

Percentage Yield:

The prepared microspheres were collected, dried at room temperature and then weighed. The percentage yield of the microspheres was calculated by measured weight of prepared microspheres was divided by the total amount of all excipients and drug used[13].

Percentage yield (%) = Amount of microspheres obtained (gm)/ Theoretical amount (gm) X 100

Determination of Particle Size:

The prepared mucoadhesive microspheres were selected randomly and their size was measured by optical microscopy (Olympus, India) method[14].

Entrapment Efficiency:

The calculated amount of the microspheres was taken and the drug was extracted from the microspheres by digesting for 24 hours with 10ml of stimulated gastric fluid (pH 1.2). After that, the solution was filtered and the filtrate was analyzed for drug content[15].

Percentage entrapment efficiency = Estimated percent drug content/ Theoretical percent drug content X 100

***In-Vitro* Drug Release Studies:**

The *in-vitro* drug release study was carried in USP XXI paddle type dissolution test apparatus using simulated gastric fluid (pH 1.2) as dissolution medium, volume of dissolution medium was 900 ml and temperature was maintained at 37 ± 1^0c throughout the study. Paddle speed was adjusted to 50 rpm. An interval of 1 hour, 10 ml of sample was withdrawn with replacement of fresh medium and analyzed for drug content by UV Visible spectrophotometer at 290 nm. All the experimental units were analyzed in triplicate and cumulative percentage drug release was calculated [15]. To understand the mechanism and kinetics of *in-vitro* drug release studies of all formulations was subjected to goodness of fit test by linear regression analysis, according to Zero order and First order kinetics equations, Higuchi's and Korsmeyer-Peppa's model[16].

Swelling Studies:

The calculated quantity of dried microspheres from each batch was placed in dissolution solution for at least 10 h. The wet weight of the swollen microspheres was determined by first blotting the microspheres with filter paper to remove surface water and then weighing them immediately. The percentage (%) swelling of microspheres was calculated using following formula such as

S = (We – Wo) / Wo x 100 % where, We = weight of the gel microspheres at equilibrium swelling; Wo = initial weight of the microspheres[17].

Stability Studies:

Best formulations were placed in borosilicate screw capped glass containers and stored in room temperature (27±2^{0}C, 60 ± 5% RH) and stability chamber (45±2^{0}C, 70 ±5 % RH) which was maintained at 90 days under ICH and WHO guidelines to assess their stability. At the end of specified day's period, samples were withdrawn and are analyzed for their drug content [18].

Morphological studies:

Surface morphology of the selected mucoadhesive microspheres of propranolol hydrochloride were determined by using Scanning Electron Microscopy (JEOL, JSM-6701 F, JAPAN) operating at 15 KV [19].

RESULTS AND DISCUSSION

IR spectral analysis:

FT-IR spectra of prepared sample were taken in the wavelength region was 600-3800 cm^{-1}at ambient temperature and the resolution was 4 cm^{-1} and compared the position and relative intensity of absorption band of physical admixtures (PSX & PSG) and pure drug shown in Figure 2&3. From the results, IR spectrum of pure drug was found to be similar to the standard IR spectrum which indicates that the obtained sample was pure propranolol hydrochloride. The IR spectra of all the pure samples and propranolol Hcl physical admixtures of suitable proportion of polymers were also subjected to the study. From these, it has been observed that the characteristic C-H stretching, C-O stretching, C=C stretching of pure propranolol hydrochloride was unchanged in the spectra of Propranolol Hcl physical admixtures and indicated that there was no significant difference in the IR spectra of pure drug compare with physical admixtures and with no changes in the peak shape and no shift of peaks. So there are no significant interactions between drug and polymers which expected to stable during the encapsulation process.

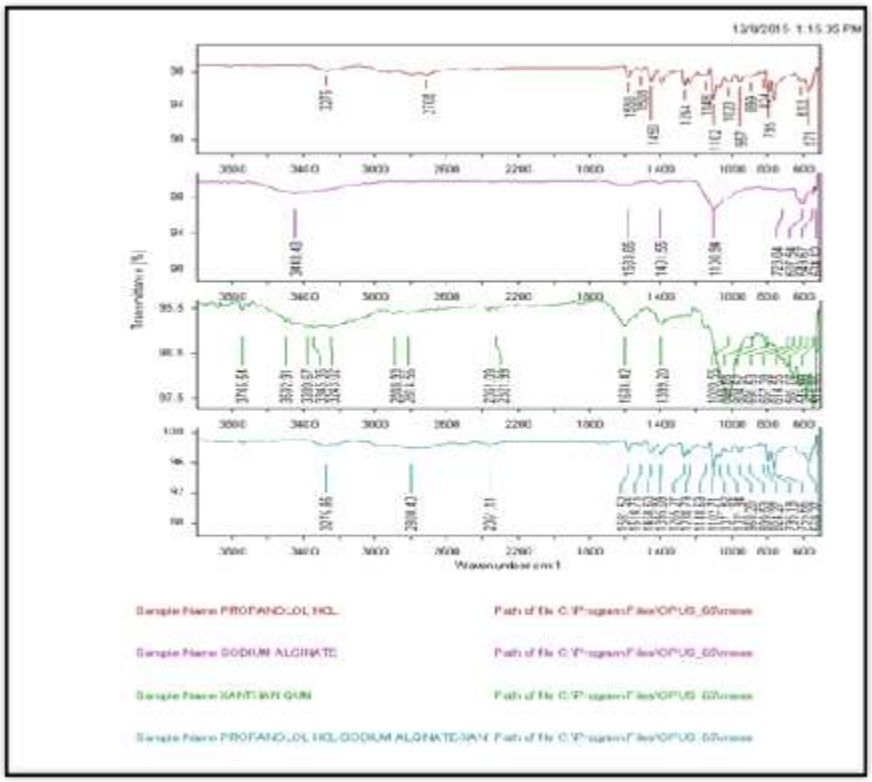

Figure 2: IR spectra studies of pure Propranolol Hcl, Sodium Alginate, Xanthan gum and Physical Admixtures of Propranolol Hcl, Sodium Alginate and Xanthan gum (PSX)

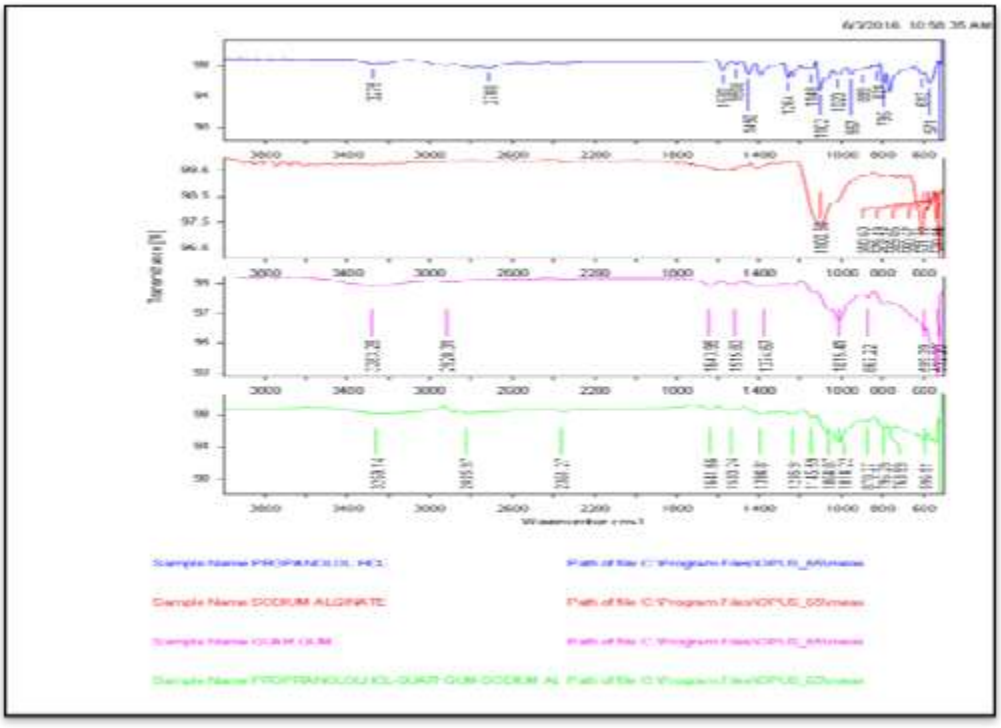

Figure 3: IR spectra studies of pure Propranolol Hcl, Sodium Alginate, Guar gum and Physical Admixtures of Propranolol Hcl, Sodium Alginate and Guar gum (PSG)

Micromeritic properties:

From Table-2, stated that the bulk density and tapped density lies in between 0.509-0.672 and 0.562-0.740 g/cm^3 indicate good packing of the microspheres. The Carr's index was lies between 5.52-12.21% indicating excellent flow characteristics. The Hausner's ratio was lies between 0.846 to 0.923 indicate good flow. Also, it was observed that the angle of repose is found to be less than 40° indicate free and good flow properties of microspheres.

Table 2: Micromeritic properties data of Propranolol Hcl Mucoadhesive Microspheres

Formulations code	Bulk density (g/cm^3)	Tapped density(g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
XG-I	0.509±0.002	0.562±0.002	5.52±0.31	0.923±0.24	$26^0.98'$ ±0.42
XG-II	0.636±0.005	0.664±0.005	9.31±0.23	0.921±0.54	$27^0.93'$±0.23
XG-III	0.656±0.003	0.682±0.003	9.66±0.51	0.910±0.33	$29^0.28'$±0.32
GG-I	0.518±0.005	0.610±0.006	7.23±0.33	0.921±0.10	$27^0.57'$±0.31
GG-II	0.639±0.004	0.724±0.003	11.05±0.21	0.874±0.34	$28^0.23'$±0.35
GG-III	0.672±0.007	0.740±0.002	12.21±0.73	0.846±0.11	$30^0.42'$±0.75

Results are mean ± S.D of three trials (n=3)

Percentage yield, Particle size and Drug entrapment:

From Table-3, the percentage yield is found between 51.06 % to 72.42 % in all formulations and it was observed that, the concentration of polymer increased, the percentage yield of the mucoadhesive microspheres was also slightly increased. The average particle size found in between 23.10±0.12 to 33.66±0.41µm. As the drug to polymer ratio was increased the mean particle size of microspheres were also increased. The significant increase in particle size may because of the increase in the viscosity of droplets which formed larger droplets and consequently larger microspheres. From the results, the entrapment efficiency was found to be in the range 37.53% to 68.28%. A maximum of 68.28% of drug entrapped in mucoadhesive microsphere (XG-III) which was prepared by 1:0.75 batches. It was observed that the entrapment efficiency increase with increasing the polymer concentration. Also the particle size increases more drug will be bound in the microspheres leading to increased entrapment efficiency[20].

Table 3: Percentage yield, Particle size and Drug entrapment of Propranolol Hcl Mucoadhesive Microspheres

Formulations	Percentage yield (%)	Particle size (µm)	Drug entrapment (%)
XG-I	62.97 ± 0.67	26.41±0.22	40.58±0.24
XG-II	66.41 ± 0.90	29.70±0.43	55.77±0.63
XG-III	72.42 ± 0.83	33.66±0.41	68.28±0.53
GG-I	51.06 ± 0.51	23.10±0.12	37.53±0.41
GG-II	61.75± 0.58	25.08±0.04	39.50±0.64
GG-III	70.40 ± 0.12	30.36±0.53	65.01±0.31

Results are mean ± S.D of three trials (n=3)

***In-vitro* drug release studies:**

The *in-vitro* drug release profile of all batches of microspheres was studied in gastric pH using 0.1N hydrochloric acid (pH 1.2). The comparative *in-vitro* drug release curve was found in Figure 4&5 and shows that the drug release from XG-III formulation is found 86.8%; similarly GG-III formulation was 89.8% at the end of dissolution studies. From the results, it was observed that, the *in-vitro* performance of mucoadhesive microspheres show prolonged and controlled release of propranolol Hcl due to the increasing the level of polymer concentration leads to increased density of polymer matrix into the microspheres which results in increased diffusional path length. This may decrease the drug release from the polymer matrix and exhibit prolonged time.

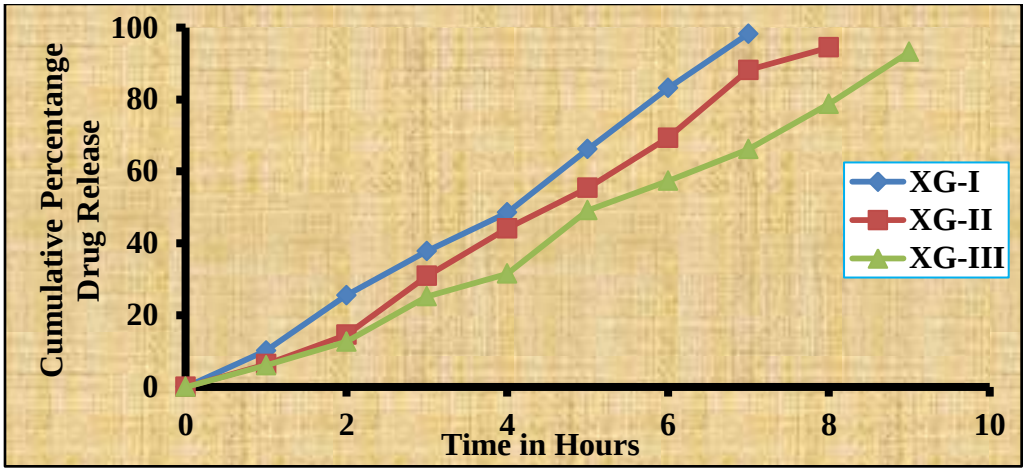

Figure 4: Comparative *in-vitro* drug release plot of Propranolol Hcl Mucoadhesive microspheres (XG-I to XG-III)

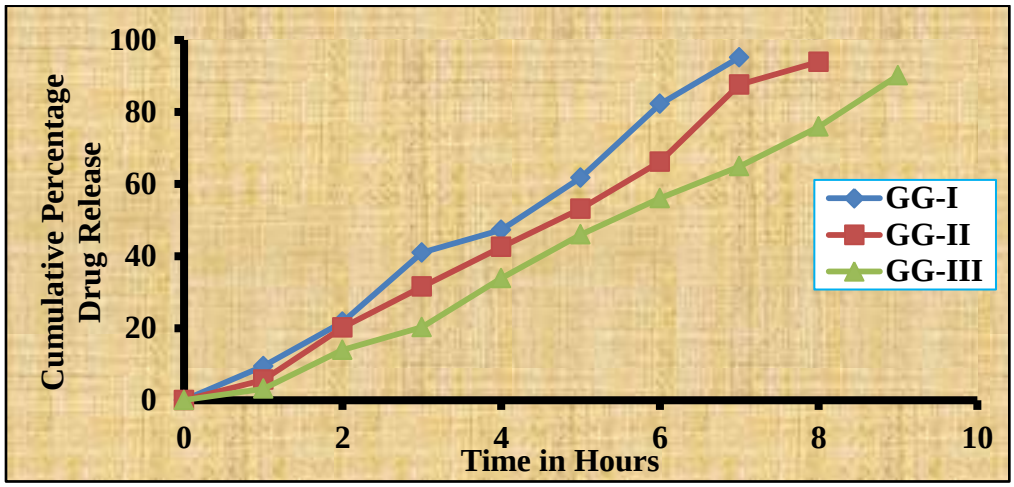

Figure 5: Comparative *in-vitro* drug release plot of Propranolol Hcl Mucoadhesive microspheres (GG-I to GG-III)

In order to understand the mechanism and kinetics of *in-vitro* drug release studies of all formulations are given in Table-4 and coefficient of correlation (r) values were computed. From the results, zero order kinetics was found to be 0.9951, 0.9911, 0.9910, & 0.9913, 0.9901, 0.9940 respectively. So the co-efficient of determination indicated that the release data was best fitted with zero order kinetics. When the drug release data was put in to Higuchi's equation, good correlation coefficient (r) values 0.9570 to 0.9690 were obtained, indicating the drug release was diffusion controlled release mechanism. The release data obtained were also put in korsmeyer-peppas model in order to find out n values, which describe the drug release mechanism. From the kinetics result data, the 'n' values of mucoadhesive microspheres were found in the range of 1.1460 to 1.4490 with correlation coefficient values ranging from 0.9940 to 0.9770, indicating good linearity. Hence, the above observations, the release of drug from mucoadhesive microspheres provide a controlled release for a period of sufficient hours and the kinetics study shows that 'r' values of all formulated batches indicate compliance with Higuchi's plot and reveals that the drug release follows non-fickian diffusion mechanism.

Table 4: Kinetic analysis data of Propranolol Hcl Mucoadhesive Microspheres

Formulations code	Release model							
	Zero order		First order		Higuchi's		Korsmeyer and peppa's	
	R	S	R	S	R	S	R	S
XG-I	0.9951	13.59	0.8211	-0.1572	0.9690	51.04	0.9940	1.1460
XG-II	0.9911	12.15	0.8852	-0.1261	0.9651	47.44	0.9942	1.3333
XG-III	0.9910	10.08	0.8640	-0.8640	0.9671	36.92	0.9961	1.2551
GG-I	0.9913	13.25	0.8741	-0.1581	0.9682	49.94	0.9922	1.1772
GG-II	0.9901	11.58	0.8933	-0.1342	0.9570	46.26	0.9771	1.2930
GG-III	0.9940	10.43	0.8791	-0.8790	0.9651	41.23	0.9770	1.4490

Correlation coefficient (r), Slope(s)

Swelling studies:

From the Table-5 results, XG-III showed highest swelling of 67.75 % attributed to the relative density of microspheres in higher polymer concentrations. The fundamentals that the increase in degree of swelling depends on the range of polymer concentration in formulation. From the results, it was observed that the xanthan gum formulations showed greater percentage and good degree of swelling index than guar gum batches.

Table 5: Swelling index of Propranolol Hcl Mucoadhesive Microspheres

Formulations code	Swelling index %)
XG-I	52.17±0.03
XG-II	61.44±0.02
XG-III	67.75±0.06
GG-I	45.01±0.01

GG-II	51.80±0.03
GG-III	56.47±0.02

Results are mean ± S.D of three trials (n=3)

Stability studies:

Best formulation of Propranolol Hcl microspheres (XG-III) based upon *in-vitro* drug release studies was taken and stored at room temperature and stability chamber and analyzed for their drug content and illustrated in Table-6. From the results, the stability studies shows that there is about 66.05 % to 67.90 % of drug present in XG-III formulation with no observable physical changes occur during the storage for three months.

Table 6: Stability studies data of Propranolol Hcl Mucoadhesive Microspheres

At the end (in days)	Physical Appearance	Percentage Drug Content (XG III) 27 ± 2^0C,60±5% RH	40 ± 2^0C,70± 5% RH
30	No change	67.90±0.54	67.14±0.52
60	No change	67.12±0.53	66.89±0.51
90	No change	66.72±0.52	66.05±0.61

Results are mean ± S.D of three trials (n=3)

Morphological studies:

The surface morphology was determined by SEM for the characterization of shape and size of mucoadhesive microspheres. Figure 6&7 shows that the prepared microspheres is completely covered with the mucoadhesive polymer and were a good specificity, spherical, uniform in shape and exhibited smooth surface. The surface smoothness of prepared microspheres was decreased by increasing the amount of gum which confirmed by SEM.

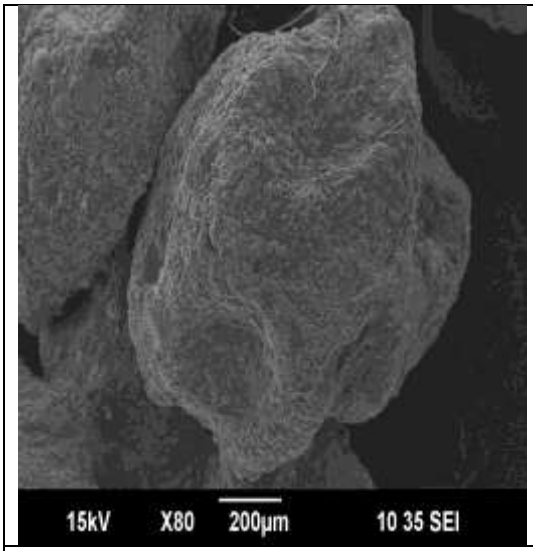

Figure 6: SEM image of Propranolol Hcl Mucoadhesive microspheres (XG-III)

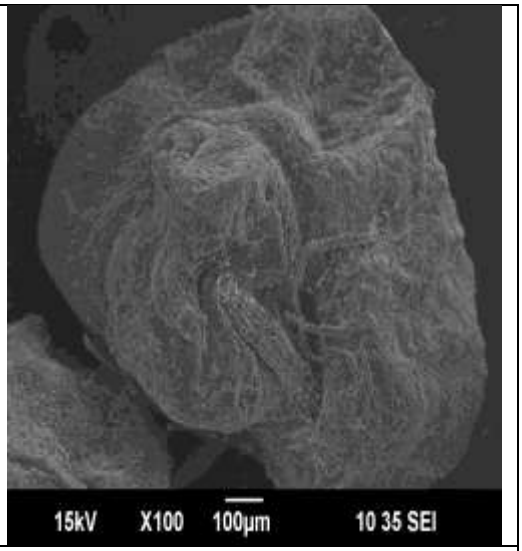

Figure 7: SEM image of Propranolol Hcl Mucoadhesive microspheres(GG-III)

CONCLUSION

Mucoadhesive microspheres loaded Propranolol Hcl is obtained by using suitable ratio's of Xanthan gum and Guar gum and the formulated microspheres might be better practical approach to achieve the retarded effect and continuously releasing the medication over extended period of time in the stomach and upper GIT with decreased GI side effect due to the less frequently of administration and all the result data's were found to be satisfactory. Hence, it's concluded that the prepared mucoadhesive microspheres can be selected for the development of gastro retentive drug delivery system for potential therapeutic uses, thereby enhance bioavailability and improve the patient compliance.

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